REMARKS

This responds to the Office Action mailed on June 30, 2008.

Claims 173, 182, 184, 200, 231, and 234 are amended; claims 178, 207-211 and 233 are canceled. Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are pending in this application.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claim 231 was rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. The amendments to claim 231 render this rejection moot.

Claims 200-201, 203 and 205-206 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. Applicant notes that claim 201 was canceled in the response filed on November 27, 2007. The amendment to claim 200, to delete "has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof," obviates the rejection of claims 200, 203 and 205-206 under § 112(1).

Therefore, withdrawal of the § 112(1) rejections is respectfully requested.

The Nonstatutory Obviousness-Type Double Patenting Rejections

Claims 173-194, 196-203, 205-211, and 231 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 153-173 of copending application Serial No. 10/729,056. As Serial No. 10/729,056 has not yet issued, a terminal disclaimer is not required at this time.

Claims 200-201 and 205-206 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587. This rejection is respectfully traversed.

Claim 8 in the '587 patent is directed to a method for lowering serum cholesterol, where a compound of formula (VI) is administered. In contrast, claim 200 is directed to a method of increasing the level of TGF-beta in a mammal afflicted with a cardiovascular indication characterized by a decreased lumen vessel diameter, wherein the administered agent is a

structural analog of tamoxifen or a pharmaceutically acceptable salt thereof, and is administered in an amount effective to elevate active TGF-beta1 levels.

Accordingly, withdrawal of the obviousness-type double patenting rejection over claim 8 in the '587 patent is respectfully requested.

The 35 U.S.C. § 102 Rejection

Claims 173-182, 186-193, 196-201, 203, 205-211, and 231 were rejected under 35 U.S.C. § 102(b) for anticipation by Ito et al. (WO 94/09764) evidenced by Schilling Immunvaskulitis Therapiewoche, 25:1157 (1975). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Ito et al. disclose the use of toremifene to treat autoimmune diseases. In particular, it is disclosed that the administration of 100 mg/kg toremifene orally every day for 13 weeks to mice with spontaneous autoimmune disease inhibited the appearance of autoreactive T cells (page 8).

Ito et al. do not teach or suggest locally administering a cytostatic dose of a compound of formula (I), e.g., to treat a cardiovascular or vascular indication characterized by a decreased lumen diameter; the use of a compound of formula (I) to increase TGF-beta levels in a diabetic mammal; the use of an agent that directly or indirectly elevates the level of active TGF-beta1 in a mammal afflicted with a cardiovascular indication characterized by a decreased lumen vessel diameter; or the use of a compound of formula (I) to treat arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy, or retinopathy.

Therefore, withdrawal of the § 102(b) rejection is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 173-181, 205-211 and 231 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 (1992)). Claims 183-185, 194, 202, 231, and 233-234 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ito et al. (WO 94/09764). Claims 173-194, 196-203 and 205-211 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang (U.S. Patent No. 5,445,941). As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Sawada et al. disclose that in order to evaluate the safety of toremifene, which is expected to be used in the treatment of breast cancer, toremifene was orally administered to female rats (pages 1 and 3 of the translation) for 52 weeks. In particular, it is noted that "[b]ecause the use of this drug is to be limited to female patients, only female rats were tested" (page 1 of translation). It is disclosed that the animals were divided into a control group and groups administered 0.01, 0.1, 1 and 10 mg/kg toremifene per day, and that the administered dose was 5 ml/mg. These amounts were based on earlier studies where a 0.7 mg/ml group showed toxic changes, including suppressed weight gain and total cholesterol reduction. Specifically, in concluding, Sawada et al. state that when toremifene was administered to female rats, "toxic changes were observed in the female reproductive system, pituitary, liver function and body weight" (page 12 of translation).

Thus, Sawada et al. teach that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. Sawada et al. also link decreased cholesterol to a change in liver function, which, in the case of tamoxifen, can be associated with liver tumor formation. See Sawada et al. at page 13. Sawada et al. is therefore teaching against the use of such dosages, due to the associated toxicity. In addition, Sawada et al. fail to teach, suggest, or imply that toremifene is or could be a therapeutic anti-cholesterol agent. In particular, Sawada et al. measured total cholesterol levels in the rats, which does not distinguish between a reduction in "good" cholesterol versus "bad" cholesterol. Moreover, based upon the disclosure of Sawada et al., it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGF-beta levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption. In addition, an abnormal estrous cycle was observed in the 0.1 mg/kg group, and uterine atrophy and the absence of an estrous cycle occurred for nearly three weeks in the 1 mg/kg group (page 9 of the translation).

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to employ toremifene citrate in 0.1 mg/kg or more including 10 mg/kg to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis. According to the Examiner, one would have been motivated to employ toremifene citrate in 0.1 mg/kg or more including 10 mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or

vascular indication such as atherosclerosis because Sawada et al. teach the administration of toremifene citrate in 0.1 mg/kg or more including 10 mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats. The Examiner continues, asserting that one would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis, and that the claimed compounds are so closely related structurally to the compounds of the reference to be structurally obvious therefrom in the absence of any unobvious or unexpected properties.

While the toxicity observed with toremifene administration, including suppressed weight gain, total cholesterol reduction, and abnormalities of the uterus and estrous cycles, may be acceptable to treat cancer, Sawada et al. do not provide the suggestion or motivation to reach the present invention, e.g., locally administering a cytostatic dose of a compound of formula (I), e.g., to treat a cardiovascular or vascular indication characterized by a decreased lumen diameter or treat arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy or retinopathy. Thus, Sawada et al. do not teach all the elements of the claims.

Moreover, Sawada et al. teach away from the use of toremifene or analogs thereof, for instance, to treat diseases other than cancer.

With respect to Ito et al., the Examiner asserts that it would have been obvious to one of ordinary skill in the art to employ toremifene and its analogs such as idoxifene or droloxifene for the treatment of angitis (small vessel disease).

Ito et al. provide no motivation to employ toremifene or any analog thereof to treat any disorder other than one associated with autoreactive T cells. Applicant directs the Examiner to page 1, lines 16-18, page 6, line 26 to page 7, line 4, and page 11, lines 22-27 of Ito et al., which disclose angitis only as associated with autoimmune diseases.

Furthermore, Ito et al. neither disclose nor suggest all of the limitations of the claims including the use of agents to treat a diabetic mammal or to treat arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy, or retinopathy.

Yang discloses screening methods to identify agents for the treatment of osteoporosis or serum lipid lowering. The method includes the use of eukaryotic cells having a promoter region of a TGF-beta gene that is a raloxifene responsive element (column 7, lines 16-32). The method identifies agents that induce expression from a raloxifene responsive element without inducing

deleterious side effects associated with current anti-osteoporosis therapy regimes (abstract). The results in Table 1 show that estradiol, raloxifene and tamoxifen induced expression from TGF-beta2 and TGF-beta3 derived promoters, not TGF-beta1 derived promoters, that were present in human osteosarcoma cells (MG63 cells). The remaining agents were screened on cells with TGF-beta3 derived promoters, i.e., MG63 cells, CHO (Chinese hamster ovary) cells or MCF-7 (breast cancer) cells.

The screening assay disclosed in Yang does not provide a reasonable expectation that an agent that elevates TGF-beta1 levels or a cytostatic dose of a compound of formula (I), would be useful to treat any disease, such as a cardiovascular or vascular indication characterized by a decreased lumen diameter.

The Examiner asserts that according to Yang, antiestrogens such as toremifene are useful for treating osteoporosis because they induce secretion of TGF-beta, and elevated serum levels of LDL, noted in women with osteoporosis, correlate with increased incidence of coronary artery disease, atherosclerosis and myocardial infarction.

The Examiner has clearly employed hindsight in concluding that one of skill in the art would link TGF-beta levels with serum LDL levels, based on Yang. Yang does not teach a relationship or functional correlation between TGF-beta levels and serum LDL levels. Rather, Yang presents methods for identifying agents that induce expression of genes linked to TGF-beta derived promoters; those agents may, in some cases, also act as anti-estrogens that possess lipid lowering properties. Based on Yang, one of skill would not be led to conclude that a relationship exists between TGF-beta levels and serum levels of LDL, and would not reach the claimed invention, e.g., <u>locally</u> administering a cytostatic dose of a compound of formula (I), e.g., to treat a cardiovascular or vascular indication characterized by a decreased lumen diameter or treat a diabetic mammal, or a method of increasing the level of TGF-beta in a mammal afflicted with a cardiovascular indication characterized by a decreased lumen vessel diameter, in which an agent that directly or indirectly <u>elevates the level of active TGF-beta1</u> in said mammal, and is a structural analog of tamoxifen or a pharmaceutically acceptable salt thereof, is administered in an effective amount.

Therefore, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date October 31, 2008 By

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 30th day of October, 2008.

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